REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of May 19, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim 1 has been amended. Claims 2-38 have been canceled. Claims 39-46 have been added. Claims 1 and 39-46 are pending in the instant application.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the addition of new claims 39-46. The subject matter of new claims 39-46 corresponds with subject matter originally found in cancelled claims 2-38. The above additions to the claims also find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 47, lines 15-19 refers to use of various types of samples and page 38, line 16 to

page 39, line 6 refers to different mass spectrometric techniques. Page 46, line 15 refers to practicing the claimed methods with a human patient. Pages 47-48 describe kits contemplated for use with the claimed methods. Lines 10-15 on page 47 refer particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Request for Rejoining of Claims

The instant application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochai*. Similarly, if the peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 of the instant application is found to be novel, methods and kits limited to its use should also be novel. Thus, in an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner enter the new claims (39-46) added herein by amendment and consider rejoining them with claims

reading on the biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1 after such claims to the biopolymer marker are found allowable.

Sequence compliance

Applicants have reviewed the entire specification including the figures and the claims for sequence disclosures. The only sequences found to be disclosed are the amino acid sequences identified as SEQ ID NOS:1-3. On page 46 of the original disclosure, the first and last amino acid residues of each of SEQ ID NOS:1-3 are shown in parentheses. When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NOS:1-3 are predicted residues as disclosed by the parentheses on page 46 of the original disclosure. Thus, no new matter is added. The first and last amino acid residues of SEQ ID NO:1 are disclosed in the Sequence Listing, however the biopolymer marker peptide identified in patient sera consists of amino acid residues 2-18 of SEQ ID NO:1. The amendments to the claims and specification limiting the marker sequences to specific amino acid residues are made for the purpose of

clarification of the use of parentheses only. The claims as herein amended limit the biopolymer marker peptide sequence to amino acid residues 2-18 of SEQ ID NO:1.

Objection to the Claims

Claim 1, as originally presented, stands objected to because of the alleged informality of having a period in the middle of the claim, specifically, after "SEQ ID NO:3".

Claim 1 has been amended to remove the extraneous period in the middle of the claim.

Accordingly, Applicants have addressed this objection to claim 1 and respectfully request that the above-mentioned objection now be withdrawn.

Rejection under 35 USC 101

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 101 because the claimed invention allegedly is directed to non-statutory subject matter. The Examiner alleges that the claims fail to include any limitations, which would distinguish the claimed polypeptide sequences from those which occur in nature.

Claim 2 has been canceled and the subject matter of claim 2 has been incorporated into amended claim 1. Claim 1 has been amended to recite an isolated biopolymer marker. As used within the instant specification (at page 20, lines 9-16), the term "isolated"

is interpreted to mean "altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original environment or both. A polypeptide, such as that claimed herein (amino acid residues 2-18 of SEQ ID NO:1), naturally present in a living organism is not "isolated", however the same polypetide separated from the co-existing materials of its natural state is "isolated". It is clear from the methods recited herein that the claimed polypeptide marker (amino acid residues 2-18 of SEQ ID NO:1)is obtained from samples which have been isolated from a patient's body, thus the claimed polypeptide is "isolated" (see page 35, lines 14-18 and page 46, lines 14-20).

Accordingly, it is respectfully submitted that the Applicants have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 1 is vague and indefinite because it is not clear whether "analyte thereof" refers to a

biopolymer marker or to SEQ ID NO:1. The Examiner states that according to the instant specification, "biopolymers" are defined as "biological molecules/macromolecules" and an "analyte" is defined as "any atom and/or molecule; including their complexes and fragment ions" (page 6, lines 15-19). The Examiner alleges that the definitions of these two terms appear to be conflicting, because one would not recognize an atom as a biopolymer.

Claim 1 has been amended and does not recite the phrase "analyte thereof". Furthermore, the phrase "analyte thereof" is not recited in any of the remaining pending claims.

Accordingly, applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner alleges that the instant specification fails to provide any guidance on how to use the disclosed SEQ ID NO:1 as a

marker or indicator of any disease state, including Alzheimers disease. The Examiner further asserts that there is no information disclosed in the instant specification which would provide evidence or sound scientific reasoning that a biopolymer marker (SEQ ID NO:1)is specifically associated with any particular disease state in general or with Alzheimers disease in particular.

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter has been incorporated into amended claim 1. Claim 1 has been limited to a specific biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) specifically diagnostic for Alzheimers disease.

Applicants provide a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptide at pages 37-40 of the instant specification. Pages 40-45 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptide. Furthermore, mass spectrometric and chromatographic techniques are well-known to one of skill in the art, thus even if specific protocols were not included within the disclosure, one of skill in the art would know how to carry out the protocols in the instant disclosure. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (see MPEP 2164.01). Additionally, Figure 1 shows that band 2 (which includes the

claimed biopolymer marker peptide) is strongly present in serum from Alzheimers disease patients (lanes 1-4 as read from the left) as compared with serum from age matched controls (lanes 5-8 as from the left) and normal human serum (lane 9). One of skill in the art would recognize from the protocols and figures disclosed in the instant specification that the claimed biopolymer marker peptide is indicative of Alzheimers disease. Thus, Applicants respectfully submit that the instant specification provides sufficient guidance on how to use the claimed biopolymer marker peptide as an indicator of Alzheimers disease.

The gel shown in Figure 1 provides evidence that the claimed biopolymer marker peptide is specifically associated with Alzheimers disease. The Examiner asserts that the instant specification fails to disclose any specific information regarding the data presented in Figure 1. Page 47, lines 15-19 discloses what types of samples can be used in the protocols of the instant invention. It is clear that the sample used in Figure 1 is a serum sample because control lane 9 (lanes are read from left to right) is pooled normal human serum (pooled NHS). Lanes 1-8 are labeled with patient numbers, thus it is clear that eight patient serum samples were run on the gel in figure 1. The control lanes (lanes 5-9)contain serum from patients who are aged-matched (lanes 5-8) with the patients having Alzheimers disease (lanes 1-4). Lane 9 contains pooled samples of normal human serum. Band 2 is strongly

present in the lanes containing serum from Alzheimers disease patients as compared with lanes containing serum from age-matched control patients and normal patients. This strong presence of band 2 is indicative of Alzheimers disease.

The Examiner asserts that the specification fails to explain the relationship between the claimed biopolymer marker peptide and a particular disease state. Applicants respectfully disagree with the Examiner's position. On page 5, lines 12-22, states that the present inventors do not attempt to develop a reference of "normal" but rather strive to specify particular markers whose presence, absence or relative strength/concentration in disease vs. normal is diagnostic of at least one specific disease state or whose up-regulation or down-regulation is predictive of at least one specific disease state. The relationship is observed from a comparison of disease spectra to normal spectra. This is a simple method of analysis that requires identification of differences in the spectra of the disease state versus the spectra of the non-disease state. Such simple analysis does not require "undue experimentation".

In order to further evidence that the claimed biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1; the 1826 dalton marker) can be used to identify patients having Alzheimers disease, Applicants herein provide the attached Declaration (and Figure) under 37 CFR 1.132. The profiles shown in the figure

attached to the declaration indicate that the claimed method can be used to distinguish individuals suffering from Alzheimers disease from those not inflicted with Alzheimers disease. The figure attached to the declaration provides side-by-side profiles (obtained using techniques of mass spectrometry) of normal human sera (top panel) versus sera from patients having Alzheimers disease (bottom panel). This profile comparison clearly evidences the absence of the 1826 dalton marker in normal human sera and thus establishes the specificity of the 1826 dalton peptide as a marker which when present in the sera is diagnostic for Alzheimers disease. The spectra in the figure were obtained from the data gathered in the original experiments and thus do not represent "new" or additional experimentation conducted after the time of the invention.

The Examiner provides references (Clark *et al.* Archives of Neurology 50:1164-1172 1993 and Motter *et al.* Annals of Neurology 38(4):643-647 1995) that indicate that a diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy. These references describe the state of the art ten years ago and the findings of the references are not set to exclusively define diagnosis of Alzheimers disease forever. In other words, just because these references state that diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy does not mean that these will be the only means of diagnosis

of Alzheimers disease forever. Additionally, references which are ten years old do not provide convincing evidence to describe the state of the art at the time that the instant invention was made and thus do not provide strong support for the Examiner's position of the lack of enablement of the instant invention. The instant inventors have developed an assay that can provide an accurate simple alternative to the diagnosis of Alzheimers disease which can lead to earlier diagnosis and more effective treatment.

Accordingly, Applicants assert that one of ordinary skill in the art when reviewing the instant specification and declaration filed herewith would recognize how to use the claimed biopolymer marker peptide (amino acid residues 2-18 of SEQ ID NO:1) as a marker for indication of Alzheimers disease. Thus, Applicants respectfully request that this rejection now be withdrawn.

Rejection under 35 USC 102(b)

Claim 1, as originally presented, stands rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Walsh ("Enzymatic Reaction Mechanisms" W.H. Freeman and Company, pages 425-426, 1977).

The Examiner states that claim 1 is directed to a biopolymer marker of SEQ ID NO:1 or at least one analyte thereof useful in indicating at least one particular disease state. An "analyte", according to the instant specification, is defined as "any atom

and/or molecule; including their complexes and fragment ions. This term may refer to a single component or a set of components (see page 6, lines 15-17). Thus, claim 1 encompasses a molecular embodiment, the structural feature of which can be an atom, or a molecule, such as an amino acid. The Examiner further states that although claim 1 is not limited to a biopolymer marker consisting of one amino acid, during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification. Therefore, the Examiner alleges that one would reasonably believe that claim 1 encompasses one amino acid, such as phenylalanine (Phe), which is present within SEQ ID NO:1, as an analyte of a biopolymer marker useful in indicating one particular disease. The Examiner alleges that Walsh describes a well-known pathological condition, phenylketonuria, which is characterized by elevated blood and urinary levels of phenylalanine. Thus, the Examiner alleges that the disclosure of Walsh meets the limitations of claim 1.

Claim 1 has been amended to recite an isolated biopolymer marker peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 diagnostic for Alzheimers disease. The term "analyte" has been removed from the claim. Claim 1, as instantly presented, recites a specific peptide (amino acid residues 2-18 of SEQ ID NO:1) with a specific function (diagnostic for Alzheimers disease). Furthermore, since "consisting of" is closed language and excludes

any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompass only this specific peptide (amino acid residues 2-18 of SEQ ID NO:1) thus excluding the single amino acid phenylalanine as described by Walsh. No where does Walsh teach the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1). Nor does Walsh teach any amino acid or peptide which is diagnostic for Alzheimers disease.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the compositions taught by Walsh and respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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